Clinical trial results:
Phase 2 Study of the Safety and Efficacy of CORT125134 in the Treatment of Endogenous Cushing's Syndrome

Summary

EudraCT number	2016-000899-23
Trial protocol	GB HU NL IT
Global end of trial date	24 September 2018

Results information

Result version number	v1 (current)
This version publication date	31 January 2020
First version publication date	31 January 2020

Trial information

Trial identification

Sponsor protocol code	CORT125134-451

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02804750
WHO universal trial number (UTN)	-
Other trial identifiers	128625: IND Number

Notes:

Sponsors

Sponsor organisation name	Corcept Therapeutics
Sponsor organisation address	149 Commonwealth Drive, Menlo Park, United States, 94025
Public contact	Medical Director, Corcept Therapeutics, +1 650 327 3270, info@corcept.com
Scientific contact	Medical Director, Corcept Therapeutics, +1 650 327 3270, info@corcept.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the safety and efficacy of CORT125134 for treatment of endogenous Cushing's syndrome. The multicenter study was conducted in the United States and in Europe.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	Italy: 14
Worldwide total number of subjects	35
EEA total number of subjects	23

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	32
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened up to 6 weeks before Day 1. A total of 67 participants were screened and 35 were enrolled.

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: Low-dose Group

Arm description:

100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4.

Arm type	Experimental
Investigational medicinal product name	CORT125134
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

Arm title	Group 2: High-dose Group

Arm description:

250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period.

Arm type	Experimental
Investigational medicinal product name	CORT125134
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

Number of subjects in period 1	Group 1: Low-dose Group	Group 2: High-dose Group
Started	17	18
Completed	17	15
Not completed	0	3
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	2

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: Low-dose Group

Arm description:

100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4.

Arm type	Experimental
Investigational medicinal product name	CORT125134
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

Arm title	Group 2: High-dose Group

Arm description:

250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period.

Arm type	Experimental
Investigational medicinal product name	CORT125134
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

Number of subjects in period 2	Group 1: Low-dose Group	Group 2: High-dose Group
Started	17	15
Completed	16	15
Not completed	1	0
Adverse event, non-fatal	1	-

Period 3

Period 3 title	Period 3
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: Low-dose Group

Arm description:

100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4.

Arm type	Experimental
Investigational medicinal product name	CORT125134
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

Arm title	Group 2: High-dose Group

Arm description:

250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period.

Arm type	Experimental
Investigational medicinal product name	CORT125134
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

Number of subjects in period 3	Group 1: Low-dose Group	Group 2: High-dose Group
Started	16	15
Completed	16	13
Not completed	0	2
Adverse event, non-fatal	-	2

Period 4

Period 4 title	Period 4
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Group 2: High-dose Group

Arm description:

250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period.

Arm type	Experimental
Investigational medicinal product name	CORT125134
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

Number of subjects in period 4[1]	Group 2: High-dose Group
Started	12
Completed	7
Not completed	5
Adverse event, non-fatal	5

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Per protocol, Group 1 did not participate in Period 4. One participant in Group 2 completed Period 3 but did not start Period 4 due to a pre-scheduled surgery. This participant is considered to have completed the study; this patient did not sign Protocol Version 7.0 allowing CORT125134 dosing at 400 mg.

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: Low-dose Group
Reporting group description:	
100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4.	
Reporting group title	Group 2: High-dose Group
Reporting group description:	
250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period.	

Reporting group values	Group 1: Low-dose Group	Group 2: High-dose Group	Total
Number of subjects	17	18	35
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	17	32
From 65-84 years	2	1	3
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	47.6	49.5	
standard deviation	± 13.62	± 13.46	-
Gender categorical Units: Subjects			
Female	9	16	25
Male	8	2	10
Hypertension			
Confirmed with a mean systolic blood pressure (BP) of 130-170 mmHg and/or a mean diastolic BP of 85-110 mmHg based on the 24-hour ambulatory BP measurement.			
Units: Subjects			
Hypertension	12	11	23
No hypertension	5	7	12
Impaired Glucose Tolerance (IGT) / Type-2 Diabetes Mellitus (T2DM)			
Either a fasting glucose > 126 mg/dL and a 2-hour Oral Glucose Tolerance Test (oGTT) result for plasma glucose ≥ 200 mg/dL at 2 hours (for T2DM), or a 2-hour oGTT result for plasma glucose in the range of ≥ 140 mg/dL to < 200 mg/dL (for IGT).			
Units: Subjects			
IGT / T2DM	13	15	28
No IGT / T2DM	4	3	7

End points

End points reporting groups

Reporting group title	Group 1: Low-dose Group

Reporting group description:

100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4.

Reporting group title	Group 2: High-dose Group

Reporting group description:

250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period.

Reporting group title	Group 1: Low-dose Group

Reporting group description:

100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4.

Reporting group title	Group 2: High-dose Group

Reporting group description:

250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period.

Reporting group title	Group 1: Low-dose Group

Reporting group description:

100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4.

Reporting group title	Group 2: High-dose Group

Reporting group description:

250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period.

Reporting group title	Group 2: High-dose Group

Reporting group description:

250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period.

Primary: Percentage of Participants With One or More Adverse Events

End point title	Percentage of Participants With One or More Adverse Events[1]

End point description:

All treatment-emergent adverse events were recorded and summarized.

End point type	Primary

End point timeframe:

Group 1: up to Week 16; Group 2: up to Week 20

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No between-group statistical comparisons were planned for safety and tolerability endpoints.

End point values	Group 1: Low-dose Group	Group 2: High-dose Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: Percentage of participants				
number (not applicable)	88.24	100		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With One or More Severe (≥Grade 3) Adverse Events

End point title	Percentage of Participants With One or More Severe (≥Grade 3) Adverse Events[2]

End point description:

All treatment-emergent adverse events with Common Terminology Criteria for Adverse Events (CTCAE) ≥Grade 3 (severe) were recorded and summarized.

End point type	Primary

End point timeframe:

Group 1: up to Week 16; Group 2: up to Week 20

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No between-group statistical comparisons were planned for safety and tolerability endpoints.

End point values	Group 1: Low-dose Group	Group 2: High-dose Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: Percentage of participants				
number (not applicable)	17.65	38.89		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Hypertension Who Experience Improvement in Blood Pressure Following Treatment With CORT125134

End point title	Percentage of Participants With Hypertension Who Experience Improvement in Blood Pressure Following Treatment With CORT125134

End point description:

Improvement in BP was defined as a participant who experiences at least a 5 mmHg decrease in mean diastolic or systolic BP from Baseline who has not taken an additional antihypertensive medication during the treatment period or increased the dosage of a concurrent antihypertensive medication. The population analyzed was all enrolled participants with hypertension at Baseline who received at least one dose of study drug and had at least one post-baseline assessment.

End point type	Secondary

End point timeframe:

Group 1: Week 12 or last observation; Group 2: Week 16, or last observation

End point values	Group 1: Low-dose Group	Group 2: High-dose Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: Percentage of participants				
number (confidence interval 95%)	41.67 (15.17 to 72.33)	63.64 (30.79 to 89.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With IGT / T2DM Who Experienced a ≥25% Reduction in AUCglucose Following Treatment With CORT125134

End point title	Percentage of Participants With IGT / T2DM Who Experienced a ≥25% Reduction in AUCglucose Following Treatment With CORT125134

End point description:

Improvement in glucose control was defined as a participant who experiences at least a 25% decrease from baseline in area under the concentration-time curve for blood glucose (AUCglucose) who has not taken an additional diabetes medication during the treatment period or increased the dosage of a concurrent diabetes medication. The population analyzed was all enrolled participants with IGT / T2DM at Baseline who received at least one dose of study drug and had at least one post-baseline assessment.

End point type	Secondary

End point timeframe:

Before and 0.5, 1, 1.5, and 2 hours after a glucose drink at Week 12 or last observation (Group 1) or Week 16 or last observation (Group 2)

End point values	Group 1: Low-dose Group	Group 2: High-dose Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	14		
Units: Percentage of participants				
number (confidence interval 95%)	23.08 (5.04 to 53.81)	0 (0 to 23.16)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Percentage of Participants With IGT / T2DM Who Experience Improvement in Glucose Control Following Treatment With CORT125134: Responder

Definition Based on Response Criteria for Phase 3 Study NCT03697109 (2018-003096-35)

End point title	Percentage of Participants With IGT / T2DM Who Experience Improvement in Glucose Control Following Treatment With CORT125134: Responder Definition Based on Response Criteria for Phase 3 Study NCT03697109 (2018-003096-35)

End point description:

Improvement in glucose control was defined as a participant who experiences 1) a hemoglobin A1c (HbA1c) that is decreased by ≥ 0.5% from baseline, 2) a 2-hour oGTT plasma glucose that is normalized (< 7.8 mmol/L) or decreased by ≥ 2.8 mmol/L from baseline, or 3) a total daily insulin dose that has decreased by ≥25% or total daily sulfonylurea dose that has decreased by ≥ 50% and an HbA1c that is unchanged or decreased from baseline. The population analyzed was all enrolled participants with IGT / T2DM at Baseline who received at least one dose of study drug and had non-missing post-baseline data collected, with exclusions based on clinical judgment and/or important protocol deviations applied on a visit and outcome level rather than a participant level.

End point type	Post-hoc

End point timeframe:

Before and 0.5, 1, 1.5, and 2 hours after a glucose drink at Week 12 or last observation (Group 1) or Week 16 or last observation (Group 2)

End point values	Group 1: Low-dose Group	Group 2: High-dose Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: Percentage of participants				
number (confidence interval 95%)	15.38 (1.92 to 45.45)	50.00 (21.09 to 78.91)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Group 1: up to Week 16; Group 2: up to Week 20	
Adverse event reporting additional description:	
All enrolled participants who received at least 1 dose of study drug	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Group 1: Low-dose Group
Reporting group description:	
100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. Period 3 was followed by a 4-week follow-up period.	
Reporting group title	Group 2: High-dose Group
Reporting group description:	
250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4.	

Serious adverse events	Group 1: Low-dose Group	Group 2: High-dose Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	4 / 18 (22.22%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Polyneuropathy			

subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myopathy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pilonidal cyst			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Group 1: Low-dose Group	Group 2: High-dose Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 17 (88.24%)	18 / 18 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 17 (17.65%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Contusion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Peripheral venous disease			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Phlebitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

Surgical and medical procedures			
Medical device removal			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	4 / 17 (23.53%)	5 / 18 (27.78%)	
occurrences (all)	6	10	
Peripheral swelling			
subjects affected / exposed	1 / 17 (5.88%)	2 / 18 (11.11%)	
occurrences (all)	2	2	
Asthenia			
subjects affected / exposed	2 / 17 (11.76%)	1 / 18 (5.56%)	
occurrences (all)	4	2	
Fatigue			
subjects affected / exposed	2 / 17 (11.76%)	2 / 18 (11.11%)	
occurrences (all)	2	2	
Adverse drug reaction			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Fat tissue increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Flushing			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Influenza like illness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Chest pain			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Application site bruise			

subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Application site irritation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	3 / 17 (17.65%)	4 / 18 (22.22%)	
occurrences (all)	3	5	
Bronchitis			
subjects affected / exposed	1 / 17 (5.88%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Wheezing			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory failure			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Psychiatric disorders			

Drug withdrawal syndrome			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Emotional distress			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
C-reactive protein increased			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Body temperature increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Glucocorticoids abnormal			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Spinal fracture			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 17 (23.53%)	5 / 18 (27.78%)	
occurrences (all)	5	9	
Somnolence			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	

Neuropathy peripheral			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Sciatica			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Cervicobrachial syndrome			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	5	
Diabetic neuropathy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hypoaesthesia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	3	
Nerve root compression			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nystagmus			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 17 (0.00%)	3 / 18 (16.67%)	
occurrences (all)	0	3	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Ear pain			

subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Cataract			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Conjunctival haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Photopsia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 17 (0.00%)	3 / 18 (16.67%)	
occurrences (all)	0	3	
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	4 / 18 (22.22%)	
occurrences (all)	0	6	
Abdominal pain upper			
subjects affected / exposed	1 / 17 (5.88%)	2 / 18 (11.11%)	
occurrences (all)	1	4	
Constipation			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	4 / 17 (23.53%)	3 / 18 (16.67%)	
occurrences (all)	7	7	
Dyspepsia			

subjects affected / exposed	1 / 17 (5.88%)	4 / 18 (22.22%)	
occurrences (all)	1	5	
Nausea			
subjects affected / exposed	3 / 17 (17.65%)	5 / 18 (27.78%)	
occurrences (all)	5	7	
Vomiting			
subjects affected / exposed	2 / 17 (11.76%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Flatulence			
subjects affected / exposed	1 / 17 (5.88%)	2 / 18 (11.11%)	
occurrences (all)	1	4	
Haemorrhoids			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gingival hyperpigmentation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 17 (11.76%)	1 / 18 (5.56%)	
occurrences (all)	4	3	
Dry skin			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Application site vesicles			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Dermatitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Erythema			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

Folliculitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hidradenitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hyperkeratosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Night sweats			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pigmentation disorder			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Skin hyperpigmentation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hyperprolactinaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	4 / 17 (23.53%)	7 / 18 (38.89%)	
occurrences (all)	11	26	
Pain in extremity			
subjects affected / exposed	4 / 17 (23.53%)	4 / 18 (22.22%)	
occurrences (all)	10	7	
Arthralgia			
subjects affected / exposed	2 / 17 (11.76%)	4 / 18 (22.22%)	
occurrences (all)	2	10	
Joint swelling			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	
occurrences (all)	1	2	
Myalgia			
subjects affected / exposed	1 / 17 (5.88%)	4 / 18 (22.22%)	
occurrences (all)	1	7	
Musculoskeletal pain			
subjects affected / exposed	0 / 17 (0.00%)	3 / 18 (16.67%)	
occurrences (all)	0	8	
Intervertebral disc disorder			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Medial tibial stress syndrome			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Muscle fatigue			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	6	
Neck pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pain in jaw			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

Muscular weakness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pilonidal cyst			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Infections and infestations			
Fungal infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Lymphangitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Candida infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Enterobacter infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Hypocalcaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Increased appetite			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2016	Amendment 2 Version 4.0: 1) clarified details of urinary free cortisol and salivary cortisol sampling times; 2) clarified the timing of oGTTs and 24-hour ambulatory blood pressure monitoring; 3) changed dose levels; 4) added dose-escalation rule; 5) specified the timing of DRC review in the study design figure; 6) updated eligibility criteria; 7) clarified the number of capsules to use and capsule packaging; 8) detail added to the dose reduction and escalation options; 9) cautioned against foods known to inhibit CYP2C8 or CYP3A4; 10) added details and requirement for completion of Patient Diary Card; 11) defined the fasting time before oGTT test; 12) clarified timing of ambulatory blood pressure measurements; 13) specified time windows for PK samples; 14) clarified dose-escalation rule; 15) clarified visit windows; 16) clarified the screening tests to be performed if a washout period is needed for participants taking Cushing medications.
16 November 2017	Version 6.0: 1) added that participants who complete 12 weeks of dosing in Group 1, and on the recommendation of the Investigator and with agreement of the Medical Monitor may proceed into Group 2 and receive the Group 3 dose-escalation scheme; 2) made modifications and clarifications to the screening procedures and the inclusion and exclusion criteria; 3) made clarifications and updates to assessment procedures; 4) made clarifications to the Statistical Analysis Plan.
15 January 2018	Version 7.0: 1) the CORT125134 400 mg dose level was added to the Group 2 dose escalation scheme; 2) extended the age range from 75 to 80 years; 3) corrected the definition of impaired glucose tolerance; 4) clarified the assessments required for participants who proceed from Group 1 to Group 2 dose escalation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported